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METHOD AND DEVICE USING MYOELECTRICAL ACTIVITY FOR OPTIMIZING A PATIENT'S VENTILATORY ASSIST

FIELD OF THE INVENTION

The present invention relates to a method and device for determining a level of ventilatory assist to a ventilator-dependent patient.

BACKGROUND OF THE INVENTION

Both the tension developed by a patient's muscle [34] and the duration of the muscle contraction [2] are factors that lead to respiratory muscle fatigue; these two factors can be expressed by indices such as the tension-time index [3] and the pressure-time product [10, 20, 32, 35]. Bellemare and Grassino [3] showed a direct inverse relationship exists between the time of endurance of a fatiguing diaphragm contraction and the rate of decay of the ratio of the high to low spectral components (H/L) of the electrical activity EAdi of the patient's diaphragm, indicating that these two values are indicative of progressive failure to sustain load. The force exerted by the muscle has been shown to be directly related to the rate of decay of the power spectrum center frequency or the rate of decay of the above mentioned ratio H/L, and the level at which this power spectrum center frequency or ratio H/L plateaus [16, 21, 28]. Such shifts in the power spectrum reflect a reduction in the muscle action potential conduction velocity [28, 38, 39], and constitute an early indication that, at the cellular level, these breathing patterns cannot be maintained indefinitely [3].

Hyperinflation, which impairs the length-tension relationship of the respiratory muscles, i.e. the transformation of the neural activation into a mechanical output or pressure, reduces the capacity of the respiratory muscles to generate pressure (neuromechanical uncoupling), unless the electrical activity EAdi of the patient's diaphragm is increased. Studies have shown that when the

inspiratory pressure, flow and duty cycle remain constant, increases in end-expiratory lung volume (EELV) promote reductions in endurance time [33, 44] and sustainable pressure [11]. In an animal model, Tzelepis et al [44] proposed that, under these conditions, diaphragm shortening would require greater excitation to generate a given sub-maximum tension, and that this increased excitation might account for the greater contractile muscle fatigability observed at shorter muscle length.

The level of partial ventilatory assist, with the aim to ensure adequate pulmonary ventilation while preserving inspiratory muscle function, is generally set on an empirical basis in the clinical setting.

It has been proposed that an optimal level of partial ventilatory assist could be determined from the lowest stable breathing frequency f_B achieved, i.e. without bradypnea or apnea. In patients, this corresponded to 16.4 bpm (breaths per minute) and was associated with a tidal volume V_T of 11.8 ml/kg. However, mechanical lung modeling in that study demonstrated that such a level of support actually resulted in a total unloading of the respiratory muscles.

Others have defined an optimal level of partial ventilatory assist as that which produces the lowest swings of transdiaphragmatic pressure P_{di} and found that this condition was associated with a breathing frequency f_B of 19.7 bpm and a tidal volume V_T of 11.7 ml/kg. The transdiaphragmatic pressure P_{di} in the latter study was used as a marker of inspiratory effort.

Jubran et al [20] defined an upper bound inspiratory pressure-time product lower than 125 cm $H_2O{\cdot}s$/min as a desirable level of inspiratory effort to be achieved during partial ventilatory assist. Although arbitrarily determined, this threshold was justified by the fact that it corresponded to a tension-time index TT_{di} well below that considered to indicate impeding inspiratory muscle fatigue. The study found a high variability in pressure-time products between patients and demonstrated that a breathing frequency f_B < 30 bpm and a tidal volume V_T

of 0.6 L were better determinants of an optimal level of inspiratory effort during partial ventilatory assist. Based on these breathing pattern findings, it is likely that the level of respiratory muscle unloading provided by this method of optimizing partial ventilatory assist was lower than that of the above discussed studies.

Brochard et al [8] defined an optimal partial ventilatory assist level as the lowest level of ventilatory assist, which when implemented, maintained the highest level of diaphragmatic electrical activation without the occurrence of fatigue as evaluated via power spectrum analysis of the electrical activity EA_{di} of the patient's diaphragm. Interestingly, such levels of partial ventilatory assist were associated with a breathing frequency f_B of 20-27 bpm and a tidal volume V_T of 8.0 ml/kg, these values being similar to those later reported by Jubran et al [20].

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided a method for determining a level of ventilatory assist to a ventilator-dependent patient, comprising: calculating a critical threshold of a respiration-related feature, wherein fatigue of a respiratory muscle of the ventilator-dependent patient develops when the critical threshold is reached by the respiration-related feature; and controlling the level of ventilatory assist to the ventilator-dependent patient in relation to the critical threshold of the respiration-related feature so as to prevent fatigue of the patient's respiratory muscle.

The present invention also relates to a device for determining a level of ventilatory assist to a ventilator-dependent patient, comprising: a calculator of a critical threshold of a respiration-related feature, wherein fatigue of a respiratory muscle of the ventilator-dependent patient develops when the critical threshold is reached by the respiration-related feature; and a controller of the level of

ventilatory assist to the ventilator-dependent patient in relation to the critical threshold of the respiration-related feature so as to prevent fatigue of the patient's respiratory muscle.

The foregoing and other objects, advantages and features of the present invention will become more apparent upon reading of the following non-restrictive description of illustrative embodiments thereof, given by way of example only with reference to the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

In the appended drawings:

Figure 1 is a schematic representation of a non-limitative example of experimental set-up for measuring diaphragm's electrical activity EAdi, esophageal pressure P_{es}, gastric pressure P_{ga}, respiratory airflow and tidal volume V_T, and for displaying on line the target transdiaphragmatic pressure P_{di} and the root-mean-square (RMS) of the diaphragm's electrical activity EAdi;

Figure 2 are illustrative examples of tracings of tidal volume V_T, diaphragm electrical activity EAdi, transdiaphragmatic pressure P_{di}, esophageal pressure P_{es}, and gastric pressure (P_{ga}) measured on a subject during "volume" maneuvers and "expulsive" maneuvers;

Figure 3 are examples of bar graphs displaying drops in center frequency CF_{di}, targeted levels of transdiaphragmatic pressure P_{di}, diaphragm pressure-time product PTP_{di} and the associated diaphragm's electrical activity EAdi observed during volume and lower-pressure expulsive and higher pressure expulsive maneuvers;

Figure 4 are examples of graphs from one representative subject showing the center frequency CF_{di}, the root-means-square (RMS) of the

diaphragm's electrical activity EAdi and the diaphragm pressure-time product PTP_{di} plotted over time during the volume maneuver (circles) and the two expulsive maneuvers at end-expiratory lung volume (EELV), one targeting a lower transdiaphragmatic pressure P_{di} (squares) and the other a higher P_{di} transdiaphragmatic pressure P_{di} (triangles);

Figure 5 is a flow chart and block diagram of a first non-restrictive illustrative embodiment of the method and device according to the present invention, for determining a level of ventilatory assist to a ventilator-dependent patient; and

Figure 6 is a flow chart and block diagram of a second non-restrictive illustrative embodiment of the method and device according to the present invention, for determining a level of ventilatory assist to a ventilator-dependent patient.

DETAILED DESCRIPTION OF THE ILLUSTRATIVE EMBODIMENTS

A study was conducted to determine in humans whether an increased electrical activity EAdi of a patient's diaphragm, with neuromechanical uncoupling, promotes greater reductions in the center frequency CF_{di} of the diaphragm's electrical activity EAdi, when the diaphragm pressure-time product PTP_{di} is kept constant. An additional aim of the study was to establish the extent to which the diaphragm pressure-time product PTP_{di} needs to be increased, in the presence of normal neuromechanical coupling, in order to reproduce the drop in center frequency CF_{di} observed with uncoupling.

More specifically, the study evaluated whether increased diaphragm activation induced by an increased lung volume promotes increased drops in the center frequency CF_{di} of the diaphragm's electrical activity EAdi when the diaphragm pressure-time product PTP_{di} is kept constant. Five healthy subjects performed runs of intermittent quasi-static diaphragmatic contractions with a

fixed breathing pattern. In separate runs, the subjects targeted transdiaphragmatic pressures P_{di} by performing end-inspiratory holds at total lung capacity with the glottis open (neuromechanical uncoupling), and at end-expiratory lung volume by performing expulsive maneuvers (no neuromechanical uncoupling). Diaphragm activation and pressures were measured with an electrode array and with balloons, respectively, mounted on an esophageal catheter. Reproduction of a transdiaphragmatic pressure P_{di} of ≈31 cm H_2O during neuromechanical uncoupling increased lung volume to 77.5% of the inspiratory capacity, increased the diaphragm's electrical activity EAdi from 25% to 61% of the maximum and resulted in a 17% greater drop in center frequency CF_{di}. In order to reproduce, in the absence of neuromechanical uncoupling, the decrease in center frequency CF_{di} observed during neuromechanical uncoupling, a two-fold increase in transdiaphragmatic pressure P_{di} and diaphragm pressure-time product PTP_{di} was required. It was concluded that a constant diaphragm pressure-time product PTP_{di} does not necessarily result in a center frequency CF_{di} of the diaphragm's electrical activity EAdi that remains stable when activation is increased.

METHODS

Subjects

Five healthy subjects (1 female, 4 males) with a mean age of 40.6 ± 8.0 years participated in the study. The study was approved by the Scientific and Ethical Committees of Sainte-Justine's Hospital and all subjects gave their informed consent.

Experimental protocol

Figure 1 is a schematic representation of a non-limitative example of experimental set-up. On the left, an esophageal catheter-mounted multi-electrode array 5 is used to measure diaphragm's electrical activity EAdi and

balloons 8 and 9 mounted on the catheter on opposite sides of the electrode array 5 are used to measure esophageal pressure P_{es} and gastric pressure P_{ga}. The catheter 6 was passed trans-nasally and positioned at the gastro-esophageal junction 10. Respiratory airflow was measured with a pneumotachograph 3 and tidal volume V_T was obtained by integrating inspiratory flow. On the right, the target transdiaphragmatic pressure P_{di} and the root-mean-square (RMS) of the diaphragm's electrical activity EAdi are displayed on line.

Referring to Figure 1, each human subject 2, while seated in an upright chair (not shown) and facing a the monitor 1 of a computer 4, performed repeated maximal inspirations to total lung capacity (TLC) in order to obtain three reproducible voluntary maximum values for the diaphragm's electrical activity EAdi. Each subject 2 was subsequently asked to perform intermittent, near-isometric diaphragmatic contractions of 10 seconds duration, separated by 5 seconds relaxation periods during which free breathing was allowed. With visual feedback of the transdiaphragmatic pressure P_{di} on the monitor 1 of the computer 4 a low level of transdiaphragmatic pressure P_{di} was targeted during two runs, while a higher level of transdiaphragmatic pressure P_{di} was targeted during a third run. The duty cycle was imposed by a sound signal, and each run lasted until a plateau in center frequency CF_{di} was reached, or until the subject was no longer able to maintain the target transdiaphragmatic pressure P_{di}.

Figure 2 are examples of tracings of tidal volume V_T, diaphragm electrical activity EAdi, transdiaphragmatic pressure P_{di}, esophageal pressure P_{es}, and gastric pressure P_{ga} measured in one subject during "volume" maneuvers and "expulsive" maneuvers performed during the hereinafter reported study. The "volume" maneuver consisted of an end-inspiratory hold at an increased lung volume, which resulted in the generation of a low P_{di} (left tracing), whereas the two expulsive maneuvers were performed at end-expiratory lung volume targeting a lower P_{di} (middle tracing) and higher P_{di} (right tracing).

In order to obtain two different levels of diaphragm's electrical activity

EAdi for the same target transdiaphragmatic pressure P_{di}, each subject 2 was instructed to perform two different maneuvers:

1. Volume maneuver: the subjects inspired close to their total lung capacity (TLC) and produced a given level of transdiaphragmatic pressure P_{di} (Figure 2; left tracing). The transdiaphragmatic pressure P_{di} was maintained at this lung volume with the glottis open.

2. Expulsive maneuver: the subjects performed expulsive maneuvers in order to generate a target transdiaphragmatic pressure P_{di}. All expulsive maneuvers were performed at end-expiratory lung volume (EELV) at lower and higher transdiaphragmatic pressures P_{di} (Figure 2, middle and right tracings).

After having initially performed a volume maneuver run, each subject 2 then performed two expulsive maneuver runs. One expulsive maneuver run targeted a transdiaphragmatic pressure P_{di} (lower pressure) similar to that observed during the volume maneuver but requiring less diaphragm's electrical activity EAdi, while another expulsive maneuver run targeted an increased transdiaphragmatic pressure P_{di} (higher pressure) to reproduce the center frequency CF_{di} observed during the volume maneuver run. The volume maneuver was subsequently repeated once for retest purpose. The subject rested for 20 minutes between subsequent runs.

Instrumentation

Using the set-up of Figure 1:

- airflow and tidal volume were measured by a computer 4 through a pneumotachograph 3;

- electrical activity EAdi of the patient's diaphragm was measured by the

computer 4 through the linear array 5 of electrodes mounted on an esophageal catheter 6 inserted through the patient's nostril (or patient's mouth) until the electrode array 5 is positioned in the gastro-esophageal junction 10 of the patient's diaphragm 7;

- esophageal P_{es} and gastric P_{ga} pressures were measured by the computer 4 through the gastric 8 and esophageal 9 balloons mounted on the catheter 6 on opposite sides of the array 5 of electrodes; and

- the transdiaphragmatic pressure P_{di} was obtained by the computer 4 by subtracting the measured esophageal pressure P_{es} from the measured gastric pressure P_{ga}.

On-line automatic processing of diaphragm's electrical activity EAdi

The diaphragm's electrical activity EAdi, more specifically a root-mean-square (RMS) EAdi signal was acquired, processed and displayed on-line using a standardized methodology [4, 36, 41]. The center frequency CF_{di} was evaluated for signal quality using established indices and criteria in accordance with a method disclosed by Sinderby et al [40]. To avoid influence of power spectral shifts on the EAdi signal strength, the RMS EAdi signal was calculated on the spectral moment of order 1 (M1) which is insensitive to conduction velocity [6] (see upper trace on the computer monitor 1. For more extensive review reference is made to Aldrich et al [1].

Off-line signal analysis

Inspiratory duration T_i, total breath duration T_{tot}, and breathing frequency f_B, diaphragm's electrical activity EAdi and pressures P_{es} and P_{ga} were determined using the transdiaphragmatic pressure P_{di}. The diaphragm pressure-time product PTP_{di} was obtained by multiplying (i) the under-the-curve area

subtended by the P_{di} signal by (ii) the breathing frequency f_B. The amplitude of the signal of the diaphragm's electrical activity EAdi was expressed as a percentage of the voluntary maximum diaphragm's electrical activity EAdi obtained from TLC maneuvers [37]. Variables were compared between each of the maneuvers performed using one-way repeated measurements analysis of variance (ANOVA) and post hoc contrasts of significant effects were performed using the Student-Newman-Keuls test. Test-retest reliability of the P_{di}, EAdi and CF_{di} values obtained during the volume and expulsive maneuvers was evaluated by calculating the interclass correlation coefficient (ICC).

RESULTS

The subjects were able to perform all maneuvers and maintain the imposed duty cycle (P=0.93; one -way ANOVA) during all protocols (Table 1).

Table 1

Breathing pattern and targeted P_{di} values during the three maneuvers performed

Volume maneuver				Expulsive maneuver Lower pressure		Expulsive maneuver Higher pressure	
Subject	**Ti/Ttot**	**VT%IC**	**Pdi**	**Ti/Ttot**	**Pdi**	**Ti/Ttot**	**Pdi**
1	0.66	89.2	47.8	0.66	45.1	0.67	77.3
2	0.66	65.6	25.3	0.67	26.6	0.66	93.3
3	0.67	68.3	10.2	0.65	11.6	0.66	39.3
4	0.67	88.8	38.6	0.66	39.8	0.64	77.3
5	0.65	75.5	34.1	0.67	35.0	0.67	50.3
Mean	0.66	77.5	31.2	0.66	31.6	0.66	67.5

(±SD)	(0.01)	(11.1)	(14.2)	(0.01)	(13.1)	(0.01)	(22.0)

Values are means for each subject of all the maneuvers performed. Ti/Ttot, duty cycle; P_{di}, transdiaphragmatic pressure; V_T, tidal volume; IC, inspiratory capacity. All subjects were able to maintain the imposed duty cycle.

Figure 3 are examples of bar graphs displaying drops in center frequency CF_{di}, targeted levels of transdiaphragmatic pressure P_{di}, diaphragm pressure-time product PTP_{di} and the associated diaphragm's electrical activity EAdi observed during the three volume and lower-pressure expulsive and higher pressure expulsive maneuvers performed in the study. The bars of the graphs of Figure 3 are average values obtained for the five subjects (± SD (Standard Deviation)).

As shown in Table 1 and Figure 3, subjects were able to achieve and maintain similar target levels of transdiaphragmatic pressure P_{di} during the volume maneuver (high lung volume) and the lower-pressure expulsive maneuver at EELV. During the volume maneuver, subjects inspired to an average of 77.5±11.1% of their inspiratory capacity. In order to generate the same diaphragm pressure-time product PTP_{di} at different lung volumes, the volume maneuver (neuromechanical uncoupling) required a diaphragm's electrical activity EAdi of 60±8% of maximum compared to 25±8% for the expulsive lower-pressure maneuver at EELV. As shown in Table 2 and Figure 3, despite a matching of the diaphragm pressure-time product PTP_{di}, the volume maneuver promoted a 17% larger drop in the center frequency CF_{di} than the expulsive low-pressure maneuver at EELV. Figure 4 are examples of graphs from one representative subject showing the center frequency CF_{di}, the root-means-square (RMS) of the diaphragm's electrical activity EAdi and the diaphragm pressure-time product PTP_{di} plotted over time during the volume maneuver (circles) and the two expulsive maneuvers at end-expiratory lung volume (EELV), one targeting a lower transdiaphragmatic pressure P_{di} (squares) and the other a higher P_{di} transdiaphragmatic pressure P_{di} (triangles). Figure 4 shows that, for the representative subject, the center frequency CF_{di} declines more rapidly and to a greater extent during the volume maneuver (circles), which

required a high diaphragm's electrical activity EAdi for a similar diaphragm pressure-time product PTP_{di}, compared to the expulsive lower-pressure maneuver (squares).

Table 2

Individual CFdi values observed at end of each maneuver

Subject	Volume maneuver	Expulsive maneuver Low pressure	Expulsive maneuver High pressure
1	68.3 ± 8.7	81.3 ± 7.9	61.6 ± 5.6
2	67.4 ±4.5	86.7 ± 8.0	70.5 ± 13.2
3	82.0 ± 12.3	94.3 ± 7.8	71.5 ± 5.0
4	72.8 ± 5.8	89.4 ± 6.1	73.4 ± 3.1
5	80.4 ± 9.3	104.1 ± 4.4	83.6 ± 5.4
Mean±SD	74.2±6.8	91.2±8.6	72.1±7.9

Values are means for each subject for each of the maneuvers performed.

In order to produce a similar drop in center frequency CF_{di} during the expulsive maneuver at EELV as was observed during the volume maneuver, more than a two-fold increase in the target transdiaphragmatic pressure P_{di} was required. This was associated with an increase in diaphragm's electrical activity EAdi from 25±8 % to 44±9% of maximum. As can be seen in Figure 4, the rate of decline of the center frequency CF_{di} was similar for the volume maneuver (circles) and the expulsive higher-pressure maneuvers (triangles).

Presented in Table 3 are the values of transdiaphragmatic pressure P_{di}, diaphragm's electrical activity EAdi and center frequency CF_{di} for the test-retest of the volume maneuver. During the retest, subjects successfully targeted a transdiaphragmatic pressure P_{di} that was similar to that generated during the initial volume maneuver (ICC=0.95). The diaphragm's electrical activity EAdi was also similar (ICC=0.93) as was the drop in center frequency CF_{di} (ICC=0.98).

Table 3

Test-retest of the volume maneuver

	$CFdi_o$			**CFdi**			**EAdi**			**Pdi**		
	(Hz)			**(Hz)**			**(% max)**			**(cm H_2O)**		
Sub-ject	**Vol 1**		**Vol 2**	**Vol 1**		**Vol 2**	**Vol 1**		**Vol 2**	**Vol 1**		**Vol 2**
1	90.4		93.1	68.3		66.2	46.5		38.1	47.8		44.6
2	102.5		108.2	67.4		65.7	42.4		44.4	38.6		38.3
3	94.7		100.3	82.0		84.7	49.8		55.0	34.1		30.7
4	99.7		99.5	72.6		72.1	51.3		50.6	36.5		35.8
Mean	96.8		100.3	72.8		71.9	66.7		65.0	25.3		29.5
(± SD)	**(5.4)**		**(6.2)**	**(6.7)**		**(8.8)**	(10.7)		(11.9)	(9.4)		(7.0)
ICC		0.94			0.98			0.93			0.95	

EAdi, diaphragm electrical activity calculated as root-mean-square; $CFdi_o$, baseline center frequency determined during resting breathing; CFdi plateau value of the center frequency at the end of the volume maneuver; P_{di}, transdiaphragmatic pressure; Vol 1, first volume maneuver performed; Vol 2, second volume maneuver performed; ICC, interclass correlation coefficient.

DISCUSSION

The study evaluated intermittent static contractions maintained at two different lung volumes, in order to examine the effect of altered neuromechanical coupling and increased diaphragm electrical activation, on diaphragm sarcolemma excitability, assessed by changes in center frequency CF_{di}. It was

found that, for a given targeted diaphragm pressure-time product PTP_{di}, the drop in center frequency CF_{di} was greater when the diaphragm's electrical activity EAdi was increased by neuromechanical uncoupling, suggesting that the level of muscle activation influences the center frequency CF_{di}.

Studies on the canine diaphragm have demonstrated that changes in center frequency CF_{di} are associated with changes in the mean action potential conduction velocity (APCV) [38], confirming previous mathematical models [29]. During muscle contractions, both center frequency CF_{di} and muscle fiber APCV depend to a smaller extent on the cable properties of the fiber [38, 39], and to a larger extent on the muscle membrane excitability [17, 18, 29, 39]. The excitability of the muscle fiber membrane is dependent on the trans-membrane gradient of potassium, and with increased muscle activation, efflux of potassium increases. In order to defend the extra-cellular potassium concentration and hence, the membrane potential, the cell depends on the re-uptake of potassium, e.g. via the ATP (Adenosine TriPhosphate) dependent sodium/potassium pump [12], and washout via the blood circulation [25], i.e. diffusion of potassium from the extra-cellular space into the blood stream. Regardless if blood flow is reduced [23, 31, 42], or the muscle activation is increased, as in the present work, the muscles' electrical activity will indicate reduced membrane excitability, by shifts in the power spectrum toward lower frequencies. The center frequency CF_{di} can also be affected by factors such as motor unit territory, number of fibers in the motor unit, dispersion in arrival times of the single contributions in the motor unit signal, dispersion in action potential conduction velocities between motor units that can cause the diaphragm's electrical activity EAdi power spectrum to shift [4, 29]. However, given that these influences are minor in healthy muscles [30] and given that the test situation did not allow for much variability in the contractile pattern, it is unlikely that these influences had more than a minor impact on the results.

In the study, a constant transdiaphragmatic pressure P_{di} was targeted with a constant duty cycle at two different lung volumes, and it was therefore

assumed that transdiaphragmatic pressure P_{di} hindrance to blood flow under those conditions remained relatively similar at the different muscle lengths [19]. However, in order to achieve the same target transdiaphragmatic pressure P_{di} at an increased lung volume, diaphragm's electrical activity EAdi was increased, which represents an increase in energy demand/consumption as well as increased metabolic output (e.g. potassium efflux) from the cell. As can be seen in Figure 3, the rate of decline of CF_{di} at increased lung volume was significantly higher than that observed when the same pressure was targeted at FRC (doubling of transdiaphragmatic pressure P_{di} at the same lung volume) with lower diaphragm's electrical activity EAdi. Vitro studies have also demonstrated that increased activation (i.e. demand), accomplished by increasing stimulation frequency of a muscle shortened to 70% of its optimum length, in order to obtain the same tension generated at optimum length, resulted in an increased fatigue in the shortened muscle [14]. The current study therefore demonstrates that the higher diaphragm activation required for generating the target transdiaphragmatic pressure P_{di} at an increased lung volume (neuromechanical uncoupling) influences the rate/extent to which center frequency CF_{di} decays. Further theoretical evidence for the impact of neuromechanical uncoupling on the center frequency CF_{di} is provided in the following description.

In the absence of neuromechanical uncoupling, an increase in transdiaphragmatic pressure P_{di} is always associated with an increase in diaphragm's electrical activity EAdi. In the above reported study, doubling of transdiaphragmatic pressure P_{di} at the same lung volume (FRC) was associated with an increase in diaphragm's electrical activity EAdi from 25% to 44% of the maximum. Beck et al [6] showed that diaphragm's electrical activity EAdi in absolute values is closely related to transdiaphragmatic pressure P_{di}, such that activation increases (i.e. energy demand increases) when pressure increases (i.e. energy supply decreases). However, this relationship is altered when the muscle length changes. In such a circumstance, the transdiaphragmatic pressure P_{di} continues to reflect diaphragm's electrical activity EAdi only when the transdiaphragmatic pressure P_{di} is normalized to the maximum

transdiaphragmatic pressure P_{di} obtained at each corresponding lung volume [6]. It was previously shown that when the same diaphragm's electrical activity EAdi is targeted at different lung volumes, the higher resulting transdiaphragmatic pressure P_{di} generated at FRC promotes a greater drop in center frequency CF_{di} than does the lower pressure produced at the higher lung volume [42]. Such results indicate that for a given neural activation, an increase in force or transdiaphragmatic pressure P_{di} reduces diaphragm excitability. Consequently, the use of the TT_{di} and pressure-time product as indices for predicting changes in the excitability of the diaphragm sarcolemma (as reflected by center frequency CF_{di}) is limited to conditions of constant neuromechanical coupling, where the diaphragm force generating capacity remains unaltered.

Consistent with previous studies [3, 16, 21, 28], doubling of the target transdiaphragmatic pressure P_{di} at FRC in the present study increased the rate of decline of the center frequency CF_{di} as well as the level to which it declined (Figures 3 and 4). This is partially explained by the increase in diaphragm's electrical activity EAdi, as discussed above. However, it is also partially explained by the fact that:

i) diaphragm contractions with a higher transdiaphragmatic pressure P_{di} tend to hinder blood flow (i.e. energy supply) relatively more than contractions producing a lower transdiaphragmatic pressure P_{di} [19]; and

ii) impaired blood flow to a muscle has the propensity to promote shifts in the electromyographic power spectrum toward lower frequencies [22, 30].

Methodological and technical aspects

In the study the contraction and relaxation periods were maintained at a fixed duration and therefore any potential influence of duty cycle on muscle

function [2, 22] was controlled for. It must be emphasized that accurate physiological measurement of the center frequency CF_{di} depends on being able to control for:

(a) changes in muscle-to-electrode distance;

(b) electrode positioning with respect to the muscle fiber direction and location;

(c) electrode configuration;

(d) signal to noise ratio;

(e) influence of cross-talk from other muscles (including the heart and the esophagus); and

(f) electrode movement-induced artifacts [7, 36, 38, 39, 40].

In the study, the technology used to measure the power spectrum of the diaphragm's electrical activity EAdi spectrum included means for minimizing these influences [1, 36, 40]. The findings that evoked muscle action potentials are influenced by changes in lung volume [5, 15] have contributed to the assumption of a potential-inherent inaccuracy of measured amplitudes of the diaphragm's electrical activity EAdi [5, 15] and the center frequency CF_{di} [5]. However, during mild voluntary muscle contractions that do not alter diaphragm membrane excitability, it has been shown that chest wall configuration/lung volume and changes in muscle length have no effect on diaphragm's electrical activity EAdi and center frequency CF_{di} [5, 6, 7, 17, 39]. Therefore the above-discussed effect of chest wall configuration/lung volume likely did not have an impact on the results.

Another factor that could have influenced the results of the study is the

difference in partitioning the esophageal and gastric pressures for the same transdiaphragmatic pressure P_{di} during the various maneuvers. In a previous study [42], where subjects targeted the same diaphragm's electrical activity EAdi at higher and lower lung volumes, greater decreases in center frequency CF_{di} were consistently observed at EELV (higher transdiaphragmatic pressure P_{di}), regardless of whether subjects performed an expulsive (i.e. transdiaphragmatic pressure P_{di} generated mainly by gastric pressure) or a Mueller maneuver (i.e. transdiaphragmatic pressure P_{di} generated mainly by esophageal pressure) at EELV [42]. In a pilot trial to that study (unpublished observations), it was found that diaphragm contractions generating identical transdiaphragmatic pressure P_{di}, duty cycle and diaphragm's electrical activity EAdi, produced the same trajectory of decrease in center frequency CF_{di}, whether subjects performed expulsive or Mueller maneuvers. Therefore, it is not believed that differences in the partitioning of the esophageal and gastric pressures during the volume and expulsive maneuvers in the current study had an effect on the outcomes observed.

Clinical implications

The results of the above reported study have direct implications to subjects or patients being weaned from mechanical ventilation. It is well known that patients undergoing a weaning trial may demonstrate dynamic changes in EELV (dynamic hyperinflation) [43], which similar to the study would alter the neuromechanical coupling of the diaphragm. In order to compensate for this uncoupling (i.e. maintain the same transdiaphragmatic pressure P_{di}), the patient would need to increase diaphragm activation. The combination of an increased activation of the patient's diaphragm, with an elevated transdiaphragmatic pressure P_{di} would, according to the present study, lead to decreased center frequency CF_{di} (excitability), and possibly an increased respiratory effort sensation [42]. Shifts in the H/L ratio of the power spectrum of the diaphragm's electrical activity EAdi have been reported in patients with respiratory failure in whom ventilatory assistance is removed [8, 13]. However, given that diaphragm

weakness is prevalent in mechanically ventilated patients [24], it remains to be determined what combined levels of diaphragm's electrical activity EAdi and transdiaphragmatic pressure P_{di} would affect center frequency CF_{di}.

CONCLUSION

The above-reported study shows that diaphragm activation can be used to determine diaphragm membrane excitability and changes in center frequency CF_{di}. Furthermore it shows that the diaphragm pressure-time product PTP_{di} and tension-time index TT_{di} cannot be considered as valid reflections of diaphragm energy consumption and/or sarcolemma excitability when neuromechanical coupling is altered.

With data from the above investigation or study, the diaphragmatic muscle force can be estimated from measurements of the diaphragm's electrical activity EAdi in two ways.

A first way for estimating the diaphragmatic muscle force uses the following equation:

$$F = \mu EAdi \qquad (1)$$

where F is the diaphragmatic muscle force, μ is a proportionality constant, and EAdi is a measure of the signal strength of the electrical activity of the patient's diaphragm. Here the square root of the first power spectral moment is used since it represents the signal strength, which has been compensated for the influence of changes in the propagation velocity of the myoelectric action potentials [29].

A second way for estimating the diaphragmatic muscle force uses the spectral changes during diaphragm contraction. For a forceful periodic muscle loading, the center frequency CFdi decreases from an initial center frequency

CF_0 to a final plateau value CF_∞ according to the equation [26]:

$$CF_\infty = CF_o(1-\kappa)T_D / [(1-\kappa)T_D + \kappa T_R] \qquad (2)$$

where κ is the duty cycle, i.e. the inspiration time in relation to the total time period, and T_R is the center frequency CF_{di} recovery time constant pertaining to an approximately exponential time curve which is rather independent of the muscle force [9]. The symbol T_D denotes the time constant for the decrease in center frequency CF_{di}, which is related to the muscle force as [27]:

$$T_D = \eta / (F - F_C) \qquad (3)$$

In this equation η is a proportionality constant and F_C is a critical force level above which muscle fatigue starts to develop. Equation (2) is rearranged to obtain the experimentally determinable quantity:

$$Q = T_R / T_D = [(1-\kappa)/\kappa]\ [(CF_0 - CF_\infty)/CF_\infty] \qquad (4)$$

Equations (3) and (4) then give:

$$F = F_C + Q\eta / T_R \qquad (5)$$

Making equal the two force estimates of equations (1) and (5) the following relation is found:

$$\alpha EAdi - \beta - Q = 0 \qquad (6)$$

where

$$\alpha = \mu T_R / \eta \qquad (7)$$

and

$$\beta = F_C T_R / \eta \qquad (8)$$

Relation (6) represents a set of three equations (for the three experimental conditions) with two unknowns. A fitting procedure with data from the following Table 4 with simultaneous minimization of the relative errors in the diaphragm's electrical activity signal strength EAdi and the quantity Q, gives the values α = 0.00417 and β = 0.0419 with a relative fitting error of 0.24.

Table 4

Experimental results and calculated values

						Force ratios			Geometric factors		
	P_{di} (cm H_2O)	EAdi (a.u.)	CF_0 (Hz)	$CF\infty$ (Hz)	Q	ϕ_I	ϕ_{II}	ϕ_m	γ_I (cm H_2O)	γ_{II} (cm H_2O)	γ_m
Volume Maneuver	31.2	60.9	100	74.2	0.175	6.12	5.20	5.66	122	144	133
Expulsive maneuver (Lower pressure)	31.6	24.9	100	91.2	0.050	2.50	2.19	2.35	303	347	325
Expulsive maneuver (Higher pressure)	67.5	44.3	100	72.1	0.196	4.45	5.69	5.07	364	285	324

P_{di}, transdiaphragmatic pressure; a.u., arbitrary units; EAdi, signal strength of the electrical activity of the diaphragm; $CFdi_o$, baseline diaphragm center frequency determined during resting breathing; CFdi, plateau value of the diaphragm center frequency at the end of the maneuver; Q, ratio of the time constants of CFdi recovery and decline, see equation (5); ϕ_I, see equation (9); ϕ_{II}, see equation (10); ϕ_m, mean of ϕ_I and ϕ_{II}; γ_I, see equation (14); γ_{II}, see equation (15); γ_m, mean of γ_I and γ_{II}.

With α and β known, the experimental values of the diaphragmatic muscle force F can be expressed in relation to the critical force level F_C for onset

of deterioration of cell excitability, i.e. the critical force level above which muscle fatigue starts to develop. The two ways to describe this are obtained by rearranging equations (1) and (7), and equation (5), respectively, which gives:

$$\phi_I = (F / F_C)_I = \alpha EAdi / \beta \qquad (9)$$

and

$$\phi_{II} = (F / F_C)_{II} = 1 + Q / \beta \qquad (10)$$

These quantities have been determined and are listed in Table 4 together with their mean values ϕ_m.

The observed transdiaphragmatic pressure P_{di} is assumed to be related to the diaphragmatic muscle force F as:

$$P_{di} = F\ G \qquad (11)$$

where G is a geometrical factor taking into account that the diaphragm muscle changes its shape with the inspired volume. This factor G is thus assumed to be the same during the expulsive maneuvers with lower or higher P_{di} production performed at end-expiratory lung volume. As with the force relations, the transdiaphragmatic pressure P_{di} can be expressed in two ways, relating to the diaphragm's electrical activity signal strength EAdi and to the fatigue induced spectral changes. Combining equations (1), (5), and (11) leads to the following relations:

$$Pdi = \mu \quad EAdi \quad G \qquad (12)$$

and

$$Pdi = (F_C + Q\eta / T_R)G \qquad (13)$$

Relations (12) and (13) can be further developed with relations (7) and (8) into the two following relations:

$$\gamma_I = (G\eta / T_R)_I = Pdi / (\alpha \quad EAdi) \qquad (14)$$

and

$$\gamma_{II} = (G\eta / T_R)_{II} = Pdi / (\beta + Q) \qquad (15)$$

Numerical values, calculated for the two expressions, are given in Table 4 together with their mean values γ_m.

From the results listed in Table 4, it can be concluded that the diaphragmatic muscle force F in relation to the critical force level F_C are approximately the same during the volume maneuver and the higher pressure expulsive maneuver, which is also reflected in their deterioration of cell excitability, expressed by the factor Q. During all conditions the diaphragmatic muscle forces F are above the critical force level F_C as shown by values of ϕ_m in Table 4. The geometrical dependence, expressed by the factor γ_m, is obviously the same during lower pressure expulsive maneuver and higher pressure expulsive maneuver, but is much less during the volume maneuver. The ratio between the γ values in the volume maneuver and the expulsive maneuvers is about 0.41. Since the η values and the T_R values are expected to be independent of the maneuvers, this means that also the factors G have the same ratio. This indicates a much lower efficiency to convert force into pressure during the volume maneuver. The tension time index TT_{di}, taking into account the timing and the pressure, is thus not sufficient to describe the complexity of the fatigue development. At least it has to be modified with a volume dependent correction factor. Better, though, are methods reflecting the deterioration of cell excitability and not the mechanical result of the contraction.

Electromyographic and mechanical methods to detect muscle fatigue

Based on the above results, techniques to determine critical levels of muscle fatigue during periodic loading (such as respiration) will be described. A number of equations relating certain physiological variables to each other are needed and they will be derived prior to the description of these techniques.

Periodic muscle load characteristics

Consider a periodic muscle loading, such as the respiratory work, in which repeated muscle contractions alternate with muscle relaxations. The periodic muscle loading is characterized by a time period T_0 and its two parts: the duration of muscle contraction T_1 and the duration of muscle relaxation T_2 where:

$$T_0 = T_1 + T_2 \qquad (16)$$

In order to simplify the equations, the duty cycle κ is determined as:

$$\kappa = T_1 / T_0 \qquad (17)$$

The mean diaphragmatic muscle force developed during the time interval T_1 is denoted F.

Myoelectric changes due to fatigue

Isometric fatiguing contractions cause the center frequency CFdi of the diaphragm's electrical activity EAdi diaphragm's electrical activity to decrease exponentially from its resting value CF_0 with a time constant T_F. During recovery the center frequency CFdi returns gradually to its normal value following an approximately exponential course, described by the recovery time constant T_R. It is observed that many other characteristics of the power spectrum of the

diaphragm's electrical activity EAdi exhibit the same dependencies such as the median frequency, the zero crossing density, the so-called hi-over-low value, etc. The recovery time constant depends mostly on the density of capillaries in the muscle and is rather insensitive to the exerted force. The fatigue time constant is strongly dependent on the force when it exceeds a certain critical level F_C. The relation is:

$$T_F = \eta / (F - F_C) \qquad \text{for } F > F_C \qquad (18a)$$

and

$$T_F \to \infty \qquad \text{for } F \leq F_C \qquad (18b)$$

The combination of repeated work and recovery events causes the center frequency CFdi to decrease from the initial value to a final plateau value CF_∞, at which there is a balance between the metabolite production during work and wash-out during recovery. The plateau value is:

$$CF_\infty = CF_0 (1 - \kappa) T_F / [(1 - \kappa) T_F + \kappa T_R] \qquad (19)$$

Introducing the notations:

$$\Delta CF = CF_0 - CF_\infty \qquad (20)$$

and

$$\varepsilon = \Delta CF / CF_0 \qquad (21)$$

Equation (19) can then be rearranged to read:

$$\kappa = 1 / [1 + (T_R / T_F)(\Delta CF / CF_\infty)] \qquad (22)$$

With the notation:

$$Q = T_R / T_F \tag{23}$$

it is found that:

$$Q = [(1 - \kappa) / \kappa]\, \Delta CF / CF_\infty \tag{24}$$

which is an experimentally measurable quantity.

Force and pressure

The diaphragmatic muscle force F can be determined for skeletal muscles working over joints without synergistic effects from other muscles. For the diaphragm muscle the force cannot be directly measured, rather the transdiaphragmatic pressure P_{di} is obtained as a proportional measure. The following relation could be used:

$$F = \mu E \tag{25}$$

where μ is a proportionality constant and E is the signal strength of the diaphragm's electrical activity EAdi, preferably based on the first spectral moment which is rather insensitive to metabolic changes caused by fatigue. The relation to the pressure is proportional but non-linear. This fact is taken into consideration by introducing the factor G(V) which is volume (V) dependent, i.e.:

$$P_{di} = F\, G(V) \tag{26}$$

Thus,

$$\mu\, G(V) = P_{di} / E \tag{27}$$

which also is an experimentally measurable quantity.

Myoelectric signal strength and spectral changes

Rearrangement of equation (18a) and insertion of equations (23) and (25) gives:

$$\alpha E - \beta - Q = 0 \tag{28}$$

where

$$\alpha = \mu T_R / \eta \tag{29}$$

and

$$\beta = F_C T_R / \eta \tag{30}$$

It can be observed that α is dependent, through the parameter μ, on the electrode geometry and placement in relation to the muscle, while the other parameters are rather constant for similar muscles.

Experiments under fatiguing conditions at any volume give corresponding values of E and Q (through the center frequency changes). A data fitting procedure (not regression) gives numerical values to α and β. With α and β known, an estimate of the diaphragmatic muscle force F can be obtained in relation to its fatigue threshold value, i.e.:

$$F / F_C = E \alpha / \beta \tag{31}$$

As long as F/F_c is smaller than one, isometric fatigue of the patient's muscle does not develop. That means that the signal strength should be lower than the critical value:

$$E < E_{ISOM} = \beta / \alpha \qquad (32)$$

For periodic muscle work, higher forces and signal levels are tolerable.

Spectral changes as indicators of tolerable concentration of metabolites

The relative spectral change ε of the diaphragm's electrical activity EAdi, defined in equation (21), is an indirect measurement of remaining concentration of metabolites in the muscle during periodic fatiguing contractions. It seems that the muscle very rapidly goes into an anaerobic metabolic state once the force is higher than F_c and that virtually all contractions above this level causes changes in the the center frequency CFdi. Therefore it is likely that a certain small value of ε is tolerable as long as it is below a certain critical level, which we denote ε_C. With this critical value introduced into equation (22) and simultaneous use of equations (18a) and (23), it can be found that a condition for long term fatigue not to occur is:

$$\kappa < 1 / \{1 + [(1 - \varepsilon_C) / \varepsilon_C]\, T_R (F - F_C) / \eta\} \qquad (33)$$

This expression can be rearranged to give the force condition:

$$F < F_C + [(1 - \kappa) / \kappa]\, [\varepsilon_C / (1 - \varepsilon_C)]\, \eta / T_R \qquad (34)$$

or, together with equation (30),

$$F < F_C \{ 1 + [(1 - \kappa) / \kappa]\, [\varepsilon_C / (1 - \varepsilon_C)] / \beta \} \qquad (35)$$

Since the force in diaphragmatic contractions cannot be simply measured, equations (33) to (35) are expressed as functions of the signal strength E and the transdiaphragmatic pressure Pdi. Use of equations (25) and (26) give for the signal strength E of the diaphragm's electrical activity EAdi:

$$\kappa < 1 / \{1 + [(1 - \varepsilon_C) / \varepsilon_C] (\alpha E - \beta)\} \quad (36)$$

and

$$E < \{\beta + [(1 - \kappa) / \kappa] [\varepsilon_C / (1 - \varepsilon_C)]\} / \alpha \quad (37)$$

and for the transdiaphragmatic pressure Pdi:

$$\kappa < 1 / \{1 + [(1 - \varepsilon_C) / \varepsilon_C] (\alpha P_{di} - \beta)\} \quad (38)$$

and

$$P_{di} < \mu G(V) \{\beta + [(1 - \kappa) / \kappa] [\varepsilon_C / (1 - \varepsilon_C)]\} \quad (39)$$

NON-RESTRICTIVE ILLUSTRATIVE EMBODIMENT OF A METHOD AND DEVICE FOR DETERMINING AN OPTIMAL LEVEL OF VENTILATORY ASSIST TO A VENTILATOR DEPENDENT PATIENT

Non-restrictive illustrative embodiments of the method and device for determining an optimal level of ventilatory assist to a ventilator-dependent patient will now be described.

First embodiment of Figure 5

Operation 501

The signal strength of the diaphragm's electrical activity EAdi is monitored through a detector 502. As illustrated in Figure 1, detector 502 may comprise, for example, a computer 4 to measure the signal strength of the electrical activity EAdi of the patient's diaphragm through a linear array 5 of

electrodes mounted on an esophageal catheter 6 inserted through the patient's nostril (or patient's mouth) until the electrode array 5 is positioned in the gastro-esophageal junction 10 of the patient's diaphragm 7.

Operation 502

A calculator 503 calculates the coefficients α and β using equation (28):

$$\alpha E - \beta - Q = 0 \qquad (28)$$

with myoelectric data from fatigue tests (calibration). Fatigue test can be performed by either reducing the level of assist, or performing a short airway occlusion, while measuring the myoelectric activity during a few inspiratory attempts. To shorten and facilitate the fatigue test the subject could be encouraged to voluntarily increase his efforts. Such a test is routinely performed to determine the maximum inspiratory airway pressure.

Operation 504

The calculator 503 calculates the duty cycle κ as described hereinabove.

Operation 505

The calculator 503 calculates estimates of a critical level of the relative spectral change ε_C of the diaphragm's electrical activity EAdi from the general experimental fact that fatigue does not occur below a duty cycle of 0.2 even at maximum muscle force and that the critical force level F_C is approximately 0.2 times the maximum force. Equation (33) then gives $\varepsilon_C \approx \beta/(\beta+8/9)$, or, since both ε_C and β are small quantities:

$$\varepsilon_C \approx \beta \qquad (40)$$

Operation 506

The calculator 503 calculates a critical signal strength of the diaphragm's electrical activity EAdi above which isometric muscle fatigue develops, using the relatiion:

$$E < E_{ISOM} = \beta / \alpha \qquad (32)$$

Operation 507

If myoelectric monitoring is used (giving signal strength and duty cycle), the calculator 503 calculates a critical signal strength of the diaphragm's electrical activity EAdi above which long term muscle fatigue develops, is calculated using equation (37):

$$E < \{\beta + [(1 - \kappa) / \kappa] [\varepsilon_C / (1 - \varepsilon_C)]\} / \alpha \qquad (37)$$

Operation 508

A controller 509 controls the ventilatory assist, for example the gain of the ventilatory assist at a level such that the signal strength of the diaphragm's electrical activity EAdi does not exceed that described in relation (37) (higher support suggest unnecessary muscle inactivation) to prevent long-term muscle fatigue to develop::

$$E < \{\beta + [(1 - \kappa) / \kappa] [\varepsilon_C / (1 - \varepsilon_C)]\} / \alpha \qquad (37)$$

However, the signal strength of the diaphragm's electrical activity EAdi should not exceed that described in equation (32) (this level indicates the level for muscle fatigue during isometric contractions) to prevent isometric muscle

fatigue to develop::

$$E < E_{ISOM} = \beta / \alpha \quad (32)$$

Second embodiment of Figure 6

Operation 601

The signal strength of the diaphragm's electrical activity EAdi is monitored through a detector 602. As illustrated in Figure 1, detector 602 may comprise, for example, a computer 4 to measure the signal strength of the electrical activity EAdi of the patient's diaphragm through a linear array 5 of electrodes mounted on an esophageal catheter 6 inserted through the patient's nostril (or patient's mouth) until the electrode array 5 is positioned in the gastro-esophageal junction 10 of the patient's diaphragm 7.

Operation 603

A detector 604 monitors the patient's transdiaphragmatic pressure P_{di}. As illustrated in Figure 1, detector 604 may comprise, for example, a computer 4 to continuously measure the transdiaphragmatic pressure P_{di} by detecting the esophageal P_{es} and gastric P_{ga} pressures through respective gastric 8 and esophageal 9 balloons mounted on the catheter 6 on opposite sides of the array 5 of electrodes, and by processing the detected esophageal P_{es} and gastric P_{ga} pressures to obtain the patient's transdiaphragmatic pressure P_{di}.

Operation 605

A calculator 606 calculates the coefficients α and β using equation (28):

$$\alpha E - \beta - Q = 0 \quad (28)$$

with myoelectric data from fatigue tests (calibration). Fatigue test can be performed by either reducing the level of assist, or performing a short airway occlusion, while measuring the myoelectric activity during a few inspiratory attempts. To shorten and facilitate the fatigue test the subject could be encouraged to voluntarily increase his efforts. Such a test is routinely performed to determine the maximum inspiratory airway pressure.

Operation 607

The calculator 606 calculates the duty cycle κ as described hereinabove.

Operation 608

The calculator 606 calculates estimates of a critical level of the relative spectral change ε_C of the diaphragm's electrical activity EAdi from the general experimental fact that fatigue does not occur below a duty cycle of 0.2 even at maximum muscle force and that the critical force level F_C is approximately 0.2 times the maximum force. Equation (33) then gives $\varepsilon_C \approx \beta/(\beta+8/9)$, or, since both ε_C and β are small quantities:

$$\varepsilon_C \approx \beta \qquad (40)$$

Operation 609

The calculator 606 calculates a critical signal strength of the diaphragm's electrical activity EAdi above which isometric muscle fatigue develops, using the relation:

$$E < E_{ISOM} = \beta / \alpha \qquad (32)$$

Operation 610

The calculator 606 calculates a critical level of the transdiaphragmatic pressure P_{di} using relation (39):

$$P_{di} < \mu G(V) \{ \beta + [(1 - \kappa) / \kappa] [\varepsilon_C / (1 - \varepsilon_C)] \} \qquad (39)$$

Operation 610 requires knowledge about the geometrical G(V) dependence. This factor G(V) can be obtained from a calibration of the experimentally measurable quantity P_{di} / E as shown in equation (27):

$$\mu G(V) = P_{di} / E \qquad (27)$$

Alternatively, geometrical dependence G(V) of inspiratory pressure can also be estimated by performing single or multiple breath airway occlusions at two lung volumes, e.g. end-inspiration and end expiration lung volumes, while the volume difference is measured by a computer with, for example, at least one flow meter (see computer 4 and pneumotachograph 3 of Figure 1).

Operation 611

A controller 612 controls the ventilatory assist, for example the gain of the ventilatory assist at a level such that:

- the monitored signal strength of the diaphragm's electrical activity EAdi does not exceed that described in relation (32) (this level indicates the level for muscle fatigue during isometric contractions) to prevent isometric muscle fatigue to develop:

$$E < E_{ISOM} = \beta / \alpha \qquad (32)$$

- the monitored patient's transdiaphragmatic pressure P_{di} does not exceed that described in relation (39) to prevent long-term muscle fatigue to develop:

$$P_{di} < \mu\, G(V)\, \{\, \beta + [(1 - \kappa)/\kappa]\, [\varepsilon_C / (1 - \varepsilon_C)]\, \} \qquad (39)$$

Although the present invention has been described hereinabove with reference to non-restrictive illustrative embodiments thereof, it should be kept in mind that these embodiments can be modified at will within the scope of the appended claims without departing from the spirit and nature of the present invention. In particular but not exclusively:

- the present invention pertains not only to CFdi and RMS but possibly to other types of measures;

- the present invention can be implemented through measurement of the electrical activity of respiration-related muscles other than the diaphragm; and

- the present invention is concerned with any method of mechanical ventilation, including negative pressure ventilation.

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